DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JUL 28 2008

Ernest Lengle, Ph.D.
Executive Director, Regulatory Affairs
Watson Laboratories, Inc.
311 Bonnie Circle
Corona, CA 92880

Re: Docket No. FDA-2008-P-0069

Dear Dr. Lengle:

This responds to the citizen petition submitted to the Food and Drug Administration (FDA or the Agency) by Watson Laboratories, Inc. (Watson), on January 30, 2008 (Petition). The petition requests that we not approve any abbreviated new drug application (ANDA) for an irinotecan hydrochloride (HCl) product with labeling that omits dosage, administration, and other information related to the use of the drug in combination therapy with 5-fluorouracil and leucovorin and/or as a component of first-line therapy. The petition contends that an ANDA that does not include information related to the use of irinotecan HCl in combination with 5-fluorouracil and leucovorin, either as a component of first-line or second-line therapy, will nonetheless be used as such and would be less safe and effective than the reference listed drug for all of its approved uses. The petition also argues that any irinotecan HCl ANDA that omits information related to the combination use with 5-fluorouracil and leucovorin should be deemed misbranded.

We have carefully reviewed the arguments in your petition. For the reasons stated below, we deny your request.

I. BACKGROUND

A. Camptosar

On June 14, 1996, FDA approved the new drug application (NDA) held by Pharmacia & Upjohn Company (now Pfizer) for Camptosar (irinotecan HCl) intravenous injection (NDA 20-571). The NDA was approved under FDA's accelerated approval provisions for treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following fluorouracil-based therapy. At the time of the NDA approval in 1996, the sponsor was granted 5 years of marketing exclusivity. At that time, only one patent, U.S. Pat. No. 4,604,463 (the '463 patent), was listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book). The '463 patent expired on August 20, 2007, and its associated period of pediatric exclusivity

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expired February 20, 2008.[1] On October 22, 1998, FDA approved a supplement that verified clinical benefit for Camptosar, demonstrating efficacy for the second-line monotherapy indication for which Camptosar had previously obtained an accelerated approval.

On April 20, 2000, 4 years after the initial approval of NDA 20-571, FDA approved a supplement to this NDA that provided for the use of Camptosar as a component of first-line therapy in combination with 5-fluorouracil and leucovorin for patients with metastatic carcinoma of the colon or rectum. The supplement received 3-year exclusivity, which expired on April 20, 2003. Two additional patents, U.S. Pat. Nos. 6,403,569 (the '569 patent) and 6,794,370 (the '370 patent), were listed in the Orange Book in 2002 and 2004, respectively. Both of these patents are method-of-use patents pertaining to irinotecan's use in combination with 5-fluorouracil and leucovorin.[2]

The current approved labeling for Camptosar includes the following in the INDICATIONS AND USAGE section:

> CAMPTOSAR Injection is indicated as a component of first-line therapy in combination with 5-fluorouracil and leucovorin for patients with metastatic carcinoma of the colon or rectum. CAMPTOSAR is also indicated for patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial fluorouracil-based therapy.

B. ANDAs

Watson's ANDA 77-219 for irinotecan was received by FDA on July 26, 2004. It contained a paragraph III certification to the '463 patent, and a paragraph IV certification to the '569 patent. It was amended on December 22, 2004, to include a paragraph IV certification to the '370 patent. Watson's labeling does not carve out the first-line therapy indication, and it includes information pertaining to the use of irinotecan as first-line therapy in combination with 5-fluorouracil and leucovorin as well as information relating to second-line use of irinotecan HCl as monotherapy. Watson was not sued on its paragraph IV certifications, and its ANDA was tentatively approved on May 4, 2007,[3] and was fully approved on February 20, 2008.

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[1] Pediatric exclusivity was granted to Camptosar in 2004.

[2] The '569 and '370 patents do not expire until 2020. The use code listed for the '569 patent is "Use in combination with 5-fluorouracil and leucovorin for the treatment of metastatic colorectal cancer where the dose of leucovorin is at least 200 milligrams per square meter." The use code listed for the '370 patent is "Use of irinotecan in combination with 5-fluorouracil and leucovorin for the treatment of metastatic colorectal cancer."

[3] *Tentative approval* means that an application otherwise meets the requirements for approval under the Federal Food, Drug, and Cosmetic Act (the Act), but cannot be approved because there is a patent or period of exclusivity that prevents full approval. Three other irinotecan ANDAs were tentatively approved after Watson's. The tentative approvals of all the irinotecan ANDAs were based on the then unexpired '463 patent and the 6-month pediatric exclusivity period that began when the patent expired.

Watson's was the first ANDA received for irinotecan. Like Watson's, all of the other ANDAs for irinotecan HCl contained a paragraph III certification to the '463 patent. Unlike Watson, however, the other ANDA applicants elected not to submit paragraph IV certifications to the '370 and '569 patents. Instead, they submitted "section viii statements" (explained in section I.C) indicating they were not seeking approval for the conditions of use covered by these method-of-use patents. Nine additional ANDAs for irinotecan HCl have been approved. The labeling for these approved ANDAs carves out information pertaining to the use of irinotecan as first-line therapy in combination with 5-fluorouracil and leucovorin, but in all other respects the labeling is essentially the same as that of Watson's product, as well as that of Camptosar.

C. The Statutory and Regulatory Basis for Patent Protection for NDAs and Labeling Differences for ANDAs

The Act and FDA regulations require that a sponsor seeking to market a new drug submit an NDA or ANDA. NDAs are submitted under section 505(b)(1) of the Act (21 U.S.C. 355(b)(1)) and approved under section 505(c) of the Act. (21 U.S.C. 355(c)). NDAs contain, among other things, extensive scientific data demonstrating the safety and effectiveness of the drug for the indication for which approval is sought. The Act and FDA regulations also require that a sponsor of an NDA submit to FDA a list of patents claiming the approved drug substance or drug product, or claiming an approved method of using the drug product described in the NDA. Specifically, section 505(b)(1) of the Act (21 U.S.C. 355(b)(1)) requires NDA applicants to file as part of the NDA "the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or *which claims a method of using such drug* and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug" (emphasis added).[4] FDA is required to publish patent information for drugs approved under section 505(c) and does so in the Orange Book (section 505(b)(1), (c)(2), and (j)(7) of the Act and 21 CFR 314.53(e)).

A drug product with an effective approval under section 505(c) is known as a *listed drug*.[5] Under provisions added to the Act by the 1984 Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendments), Public Law No. 98-417, 98 Stat.

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[4] Section 505(c)(2) of the Act imposes an additional patent submission requirement on holders of approved NDAs when those holders subsequently obtain new patent information that could not have been submitted with the NDA.

[5] Under 21 CFR 314.3(b), "[*l*]*isted drug* means a new drug product that has an effective approval under section 505(c) of the act for safety and effectiveness or under section 505(j) of the act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness." A listed drug is identified as having an effective approval in the Orange Book, which includes patent information for each approved drug (§ 314.53(e)).

1585, the Act permits submission of ANDAs for approval of generic[6] versions of listed drugs (see section 505(j) of the Act). The ANDA process shortens the time and effort needed for approval by, among other things, allowing an ANDA applicant to rely on FDA's previous finding of safety and effectiveness for a listed drug rather than requiring the ANDA applicant to independently demonstrate the safety and effectiveness of its proposed drug. To rely on such a finding, the ANDA applicant must show that its proposed drug product is the same as the listed drug in many respects (including active ingredient, dosage form, strength, and route of administration), and that its product is bioequivalent to the listed drug.

Each ANDA applicant must identify the listed drug on which it seeks to rely for approval. As described in more detail below, the timing of ANDA approval depends on, among other things, the intellectual property protections for the listed drug the ANDA references and whether the ANDA applicant challenges those protections (see section 505(b), (c), (j)(2)(A)(vii), and (j)(5)(B) of the Act).[7] In general, an ANDA may not obtain final approval until listed patents submitted before ANDA submission and marketing exclusivity for the listed drug have expired or until the NDA holder and patent owner(s) for the relevant patents have had the opportunity to defend their patent rights in court.

Specifically, with respect to each patent submitted by the sponsor for the listed drug and listed in the Orange Book, the ANDA applicant generally must submit to FDA one of four specified certifications under section 505(j)(2)(A)(vii) of the Act. The certification must state one of the following:

(I) That the required patent information relating to such patent has not been filed (Paragraph I certification)
(II) That such patent has expired (Paragraph II certification)
(III) That the patent will expire on a particular date (Paragraph III certification)
(IV) That such patent is invalid or will not be infringed by the drug for which approval is being sought (Paragraph IV certification)

The purpose of these certifications is "to give notice, if necessary, to the patent holder so that any legal disputes regarding the scope of the patent and the possibility of infringement can be resolved as quickly as possible" (*Torpharm, Inc. v. Thompson*, 260 F. Supp. 2d 69, 71 (D.D.C. 2003)).

If an applicant files a paragraph I or II certification, the patent in question will not delay ANDA approval. If an applicant files a paragraph III certification (as did all of the

[6] Although the term *generic* is not defined in the Federal Food, Drug, and Cosmetic Act (the Act) or FDA's regulations, it is used in this petition response to refer to drug products for which approval is sought in an ANDA submitted under section 505(j) of the Act (21 U.S.C. 355(j)).

[7] Relevant intellectual property protections affecting the timing of ANDA approval include marketing exclusivity and listed patent protection for the listed drug. Marketing exclusivity is not at issue here, so this response does not address the effect of exclusivity on ANDA approval but focuses, instead, on relevant patent protection.

irinotecan ANDA applicants with respect to the '463 patent), the applicant agrees to wait until the relevant patent has expired before seeking full effective approval of its ANDA.

If, however, an applicant wishes to seek approval of its ANDA before a listed patent has expired by challenging the validity or enforceability of a patent or claiming that a patent would not be infringed by the product proposed in the ANDA, the applicant must submit a paragraph IV certification to FDA. The applicant filing a paragraph IV certification must also provide a notice to the NDA holder and the patent owner stating that the application has been submitted and explaining the factual and legal bases for the applicant's opinion that the patent is invalid or not infringed (see section 505(b)(2)(B) and (j)(2)(B) of the Act).

The filing of a paragraph IV certification "for a drug claimed in a patent or the use of which is claimed in a patent" is an act of patent infringement (35 U.S.C. 271(e)(2)(A)). For those patents listed in the Orange Book at the time of the original submission of the ANDA, if the patent owner or NDA holder brings a patent infringement suit against the ANDA applicant within 45 days of the date it received notice of the paragraph IV certification, the approval of the ANDA will be stayed for 30 months from the date of such receipt by the patent owner and NDA holder, unless a court decision is reached earlier in the patent case or the patent court otherwise orders a longer or shorter period (see section 505(c)(3)(C) and (j)(5)(B)(iii) of the Act). When the 30 months have expired, the patent ceases to be a barrier to final ANDA approval, even if the patent litigation is ongoing. Similarly, if the NDA holder and patent owner receive notice of a paragraph IV certification and decline to sue within 45 days of receipt of notice, the patent will not be a barrier to ANDA approval (the situation for Watson's ANDA with respect to the '370 and '569 patents).

These paragraph I, II, III, and IV certifications are not the only manner in which an ANDA applicant may address all relevant patents. An ANDA applicant seeking to omit an approved method of use covered by a listed patent need not file a paragraph I to IV certification for that patent. Instead, the applicant may submit a *section viii statement* acknowledging that a given method-of-use patent has been listed, but stating that the patent at issue does not claim a use for which the applicant seeks approval (see section 505(j)(2)(A)(viii) of the Act). Specifically, section 505(j)(2)(A)(viii) of the Act provides that "if with respect to the listed drug referred to in [section 505(j)(2)(A)(i)] information was filed under subsection (b) or (c) for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, [the ANDA must contain] a statement that the method of use patent does not claim such a use." Such a statement requires the ANDA applicant to omit from its labeling information pertaining to the protected use (21 CFR 314.92(a)(1) and 314.94(a)(12)(iii)). If an ANDA applicant files a section viii statement, the patent claiming the protected method of use will not serve as a barrier to ANDA approval.[8]

[8] The Agency's interpretation of the plain language of the Act is further supported by Congressional intent as evidenced by the passage below:

> . . .The [ANDA] applicant need not seek approval for all of the indications for

FDA implementing regulations at § 314.94(a)(12)(iii) describe the applicability of the section viii statement. Section 314.94(a)(12)(iii) states the following:

> If patent information is submitted under section 505(b) or (c) of the [A]ct and § 314.53 for a patent claiming a method of using the listed drug, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent, [the ANDA applicant must submit] a statement explaining that the method of use patent does not claim any of the proposed indications.[9]

Accordingly, FDA regulations also expressly recognize that by submitting a section viii statement, an ANDA applicant may omit from the proposed labeling a method of use protected by a listed patent, and therefore need not seek approval for that use.[10]

The right to file a section viii statement and carve out from labeling method-of-use information protected by a patent has been upheld by the courts. Thus, in *Purepac Pharmaceutical Company v. Thompson*, 354 F.3d 877 (D.C. Cir. 2004), the D.C. Circuit stated that a "section viii statement indicates that a patent poses no bar to approval of an ANDA because the applicant seeks to market the drug for a use other than the one encompassed by the patent" (id. at 880). Similarly, in *Torpharm*, 260 F. Supp. 2d at 73,

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> which the listed drug has been approved. For example, if the listed drug has been approved for hypertension and angina pectoris, and if the indication for hypertension is protected by patent, then the applicant could seek approval for only the angina pectoris indication.

H.R. Rep. No. 857 (Part I), 98th Cong., 2d sess. 21.

[9] FDA regulations implementing this statutory provision use the term *indications* to refer to information an ANDA applicant omits from its labeling in the context of submitting a statement that a protected use of a drug is not claimed in a listed patent (§ 314.94(a)(12)(iii)). However, the preambles for the proposed rule and final rule on patent and exclusivity provisions related to ANDA approval express no intent to distinguish between method of use and indication, using the terms interchangeably (see, e.g., 59 FR 50338 at 50347 (October 3, 1994)). Moreover, the preamble to the final rule emphasizes that an ANDA applicant does not have the option of choosing between a paragraph IV certification and a section viii statement; where the labeling does not include the indication, only the section viii statement is appropriate (id.). The preamble to the proposed rule states that where "the labeling for the applicant's proposed drug product does not include any indications that are covered by the use patent," the ANDA applicant would submit a section viii statement rather than a paragraph IV certification (54 FR 28872 at 28886 (July 10, 1989)).

[10] See also the final rule titled *Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not Be Infringed*, 68 FR 36676 (June 18, 2003). In the preamble to this final rule, we stated that the section viii statement permits an ANDA applicant to "avoid certifying to a patent by stating that it is not seeking approval for the use claimed in the listed patent" (68 FR 36676 at 36682). We stated, "[o]ur position has been that, for an ANDA applicant to file a section viii statement, it must 'carve-out' from the proposed ANDA labeling, the labeling protected by the listed patent" (id.).

the D.C. District Court stated that a section viii statement "avers that the patent in question has been listed, but does not claim a use for which the applicant seeks FDA approval." These courts have upheld the Agency's interpretation that an ANDA applicant may choose not to seek approval for a method of use protected by a listed patent, and under those circumstances, that patent will not be a barrier to ANDA approval.

Thus, under the procedures established in the Hatch-Waxman Amendments, an ANDA will not be approved until all patents listed at the time the ANDA was submitted have (1) expired, (2) been successfully challenged, (3) been subject to a paragraph IV certification pursuant to which the patent owner or NDA holder has declined to sue within 45 days, (4) been subject to a paragraph IV certification that led to a lawsuit within 45 days and a 30-month stay that has since expired, or (5) are subject to a section viii statement and a corresponding labeling carve-out.

D. Requirements Regarding ANDA Labeling

Section 505(j)(2)(A)(i) of the Act requires that an ANDA contain "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a [listed drug]." This language reflects Congress' intent that the generic drug be safe and effective for each "condition of use" prescribed, recommended, or suggested in the generic drug labeling. However, it does not require that an ANDA be approved for each condition of use for which the reference listed drug is approved. In § 314.92(a)(1), FDA has explicitly stated that a proposed generic drug product must have the same conditions of use as the listed drug, except that "conditions of use for which approval cannot be granted because of . . . an existing *patent* may be omitted" (emphasis added).

The Act also requires that an ANDA contain "information to show that the labeling proposed for the new [generic] drug is the same as the labeling approved for the listed drug. . . except for changes required because of differences approved under a petition filed under [section 505(j)(2)(C) of the Act] or because the new drug and the listed drug are produced or distributed by different manufacturers" (section 505(j)(2)(A)(v) of the Act). A parallel provision appears in section 505(j)(4)(G) of the Act.[11]

Similarly, the regulations at § 314.94(a)(8)(iv) require the following:

> Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the [generic] drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 [21 CFR

[11] Section 505(j)(4)(G) of the Act provides that FDA must approve an ANDA unless, among other things, "the information submitted in the application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for [the reference listed drug] except for changes required because of differences approved under [an ANDA suitability petition] or because the drug and the listed drug are produced or distributed by different manufacturers."

> 314.93] or because the drug product and the reference listed drug are produced or distributed by different manufacturers.

Section 314.94(a)(8)(iv) sets forth examples of permissible differences in labeling that may result because the generic drug product and reference listed drug are produced or distributed by different manufacturers. These differences include the following:

> . . . differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or *omission of an indication or other aspect of labeling protected by patent* [emphasis added] or accorded exclusivity under section 505(j)(4)(D) of the Act.[12]

The regulations at 21 CFR 314.127(a)(7) further provide that to approve an ANDA containing proposed labeling that omits "aspects of the listed drug's labeling [because those aspects] are *protected by patent* [emphasis added]," we must find that the "differences do not render the proposed drug product less safe or effective than the listed drug for all remaining non-protected conditions of use."

Relevant case law affirms an ANDA applicant's ability to carve out protected labeling without violating the "same labeling" requirement. For example, in *Bristol Myers Squibb* v. *Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996), the D.C. Circuit ruled that "the statute expresses the legislature's concern that the new generic be safe and effective for each indication that will appear on its label; whether the label for the new generic lists every indication approved for the use of the pioneer is a matter of indifference." Similarly, in *Sigma-Tau Pharmaceuticals, Inc.* v. *Schwetz*, 288 F.3d 141, 148, fn. 3 (4th Cir. 2002), the Fourth Circuit upheld the right of an ANDA applicant to carve out an indication protected by orphan drug exclusivity as a permissible difference due to difference in manufacturer. Thus, under the statute, regulations, and applicable case law, the carve-out of patent-protected labeling is generally permitted as a permissible difference due to difference in manufacturer if the omission does not render the proposed drug product less safe or effective for the conditions of use that remain in the labeling.

II. ANALYSIS

In your petition, you recognize that other ANDA applicants may submit section viii statements and seek to omit from their labeling information relating to the use of irinotecan in combination with 5-fluorouracil and leucovorin (Petition at 4). You argue, however, that "such omissions are inappropriate in light of significant safety concerns and the relevant inquiry under 21 CFR 314.127(a)(7)" (Petition at 5).

On a number of occasions, we have affirmed our authority to approve ANDAs with carved-out labeling. For example, in our April 6, 2004, response to the citizen petition in

[12] We note that, due to a series of amendments to the Act, the reference in § 314.94(a)(8)(iv) to section 505(j)(4)(D) of the Act corresponds to current section 505(j)(5)(F) of the Act.

Docket No. 2003P-0321/CP1,[13] we affirmed our authority to approve ANDAs for ribavirin with labeling that omits protected information and rejected arguments similar to the ones you are making here. We reiterated this position recently in our March 13, 2008, response to a citizen petition in Docket No. 2006P-0410/CP1 concerning ANDAs for amifostine with a protected indication carved out,[14] in our April 25, 2008, response to a citizen petition in Docket No. FDA-2007-P-0169 concerning ANDAs for dronabinol,[15] and in our June 18, 2008, response to a citizen petition in Docket No. FDA-2008-P-0304 concerning ANDAs for ramipril.[16] In rejecting your arguments as discussed below, we again reaffirm our authority to approve generic drug products with carved-out labeling, and we deny your specific request that we not approve any ANDA for irinotecan whose labeling omits information on the use of the drug as a component of first-line therapy and/or omits from its labeling any other information on the combination use of irinotecan with 5-fluorouracil and leucovorin.

A. Omission of the Protected Indication from Generic Irinotecan Labeling Does Not Render Irinotecan Less Safe and Effective for the Remaining, Non-Protected Conditions of Use.

You claim that if information on the use of irinotecan in combination with 5-fluorouracil and leucovorin, including relevant dosage and administration instructions, drug-drug interactions, warnings, and precautions, is omitted from the label, this drug will be less safe and effective than Camptosar for its remaining approved use (Petition at 2-3). You state that the approved use of irinotecan as a second-line therapy does not foreclose its use in combination with 5-fluorouracil and leucovorin and that it is commonly prescribed in combination as part of a second-line therapy (Petition at 7-8, 11). You also state that it is important for physicians with less experience with irinotecan to know the established regimens and side-effects given the vast number and complexity of doses and schedules of combinations that are used to treat metastatic colorectal cancer and considering that the combination-agent dosage varies greatly from the single-agent dosage schedules (Petition at 9, 11). Finally, you claim that, because irinotecan is prescribed, dispensed, and administered to a majority of patients in combination with 5-fluorouracil and leucovorin, it is crucial to include on all ANDA labels the same warnings that are included on the Camptosar label (Petition at 12).

As noted above, an ANDA may be approved after omitting a patent-protected condition of use, if omission of the protected information does not render the application less safe

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[13] April 6, 2004, letter from Steven K. Galson, Acting Director, Center for Drug Evaluation and Research, to David M. Fox, Docket No. 2003P-0321/CP1 (Ribavirin Response Letter).

[14] March 13, 2008, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to William C. Bertrand, Jr., Docket No. 2006P-0410/CP1 (Amifostine Response Letter).

[15] April 25, 2008, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to Victor Raczkowski, M.D., Docket No. FDA-2007-P-0169 (Dronabinol Response Letter).

[16] June 18, 2008, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to Thomas K. Rogers, Docket No. FDA-2008-P-0304 (Ramipril Response Letter).

or effective for the remaining, *non-protected* conditions of use. FDA has concluded that when information regarding the combination use of irinotecan with 5-fluorouracil and leucovorin is carved out, generic irinotecan will remain safe and effective for the remaining, non-protected conditions of use.

When information relating to the protected, first-line combination use is removed from the irinotecan labeling, the only information that will appear in the generic labeling will be information regarding the non-protected, second-line use of irinotecan as monotherapy for persons with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial fluorouracil-based therapy. Although a significant amount of information relating to the first line combination use will be carved out of the generic labeling, including certain precautions regarding use of the combination therapy regimen, this omitted information relates to use of irinotecan as combination therapy and is not necessary for the safety or effectiveness of irinotecan as monotherapy for persons with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial fluorouracil-based therapy.[17]

The DOSING AND ADMINISTRATION section of the generic irinotecan labeling will include all of the information necessary for proper dosing for the approved second-line use. Although the starting dose for the monotherapy is higher than that of the combination therapy, the generic labeling describing the second-line indication for use as monotherapy will be the same as the Camptosar labeling for that indication. Similarly, the ADVERSE EVENTS section of the generic irinotecan labeling will include the adverse events associated with this second-line use as they are described in the Camptosar labeling.

Moreover, the labeling of generic irinotecan will be essentially the same as the labeling with which Camptosar was originally approved. Camptosar was safely marketed with only this labeling for approximately 4 years (before the supplement for the combination use as first-line therapy was approved) and, of course, continues to include this information in its labeling today.

You maintain that we should not approve a generic irinotecan product without the carved-out first-line indication given that "physicians will still prescribe and pharmacists will still dispense generic irinotecan as a component of first-line therapy in combination with 5-fluorouracil and leucovorin under state substitution laws" (Petition at 5-6). You note that as irinotecan becomes more affordable, its combination use will increase dramatically and it is important to promote this use because such use has been shown to increase survival rates (Petition at 6). Thus, you appear to be suggesting that we are obligated to look beyond the approved labeling for the generic product and consider how

[17] The General subsection of the WARNINGS section of the labeling will retain information from the Camptosar labeling warning against the unapproved use of irinotecan in combination with the "Mayo Clinic" regimen of 5-fluorouracil and leucovorin. The General subsection warns against such use because of reports of increased toxicity associated with this regimen. Irinotecan in combination with the "Mayo Clinic" regimen of 5-fluorouracil and leucovorin is not one of the two irinotecan, 5-fluorouracil, and leucovorin regimens approved for Camptosar and, therefore, it will not be approved for any generic irinotecan referencing Camptosar.

the product is likely to be prescribed off-label by physicians or dispensed by pharmacists.

As noted in section I.C of this response, the Act and FDA regulations give us the authority to approve a generic drug product whose labeling carves out an indication approved for the reference listed drug, and the courts have recognized this authority. Moreover, the Fourth Circuit in *Sigma-Tau* rejected a "foreseeable use" argument as a bar to generic drug approvals. In *Sigma-Tau,* the innovator (Sigma-Tau) challenged FDA approval of generic versions of Carnitor (levocarnitine) by arguing that the generic levocarnitine drugs were intended for use in the treatment of both the orphan-protected (end stage renal disease (ESRD)) and unprotected (inborn metabolic disorders) indications for Carnitor—despite the fact that the generic levocarnitine drug labeling omitted the orphan-protected, ESRD indication. Sigma-Tau maintained that if we had properly applied our intended-use regulation at 21 CFR 201.128, we would have concluded that the generic levocarnitine products were intended for treatment of ESRD patients. Sigma-Tau argued that the court should consider "'compelling, readily available, objective evidence of the generics' intended use,' such as market data for Carnitor [levocarnitine], dosage forms, and federal drug reimbursement policies . . ." (288 F.3d at 145).

The court stated that the intended-use inquiry urged by Sigma-Tau might evolve into a foreseeable use test, which could mean that once we approve an orphan drug for a protected indication, "generic competitors might be prohibited from entering the market for almost any use" (288 F.3d at 147). The court further stated that Sigma-Tau's argument might extend exclusivity beyond what Congress intended and "frustrate the longstanding practice of Congress, the FDA, and the courts not to interfere with physicians' judgments and their prescription of drugs for off-label uses" (id. at 147 (citations omitted)). The court asserted that a "foreseeable off-label use [theory] to bar the approval of generic drugs, even for unprotected indications . . . [would add] a huge evidentiary hurdle to the generic drug approval process [and] would be profoundly anticompetitive" (id. at 147). Accordingly, the court concluded that the statutory scheme permitted an ANDA applicant to carve out a protected indication even when it is likely that the generic drug, once approved, will be used off-label for that indication.

The existence of state generic drug substitution laws, which might require the substitution of a generic irinotecan for Camptosar, also provides no basis for refusing to approve an irinotecan ANDA. We acknowledge that in some states a generic irinotecan product might be substituted for Camptosar even when the drug is intended to be used in combination with 5-fluororacil and leucovorin, but we have no control over the operation of these substitution laws. In *Bristol-Myers Squibb*, the D.C. Circuit recognized that the existence of "some state laws and health insurers that mandate substitution of generic drugs" could diminish the value of marketing protection given to the manufacturers of pioneer drugs under the Act (91 F.3d at 1500). Despite this, the court upheld FDA's interpretation of the Act and implementing regulations (e.g., §§ 314.94(a)(8)(iv) and 314.127(a)(7)) as permitting the Agency to approve an ANDA for a generic drug with labeling that omitted exclusivity-protected indications (and corresponding indication-specific dosing information) for which the innovator drug was approved. The court

stated that the potential diminution in marketing protection was "not a sufficient basis upon which to conclude that Congress intended to confer upon the manufacturers of pioneer drugs the much broader protection" which would be conferred if we could not approve generic drug products with carved-out indications (id.). Thus, the fact that state substitution laws may result in the dispensing of generic irinotecan for the protected combination-use provides no basis for denying approval of an irinotecan ANDA.

Our approval of an ANDA for irinotecan with information on combination-use omitted also would be consistent with our approvals of other generic drug products with carved-out indications and conditions of use. For example, in *Bristol-Myers Squibb*, we approved generic captopril with labeling that excluded two protected indications and corresponding protected, indication-specific dosing information. We did so even though the dosing and administration for the approved generic use was twice as high as the dosing for the carved-out indication. The D.C. Circuit held that omission of the indications protected by exclusivity was a difference in labeling "required . . . because the drug and the listed drug are produced or distributed by different manufacturers" within the meaning of the Act (91 F.3d at 1500). Other examples of generic drug products with protected labeling carved out include the following:

- Tramadol with labeling that omitted a protected slower titration schedule but included information on the unprotected faster titration schedule also appearing in the labeling of the innovator product

- Oxandrolone with labeling that omitted protected information on geriatric use

- Ribavirin with labeling that omitted use of the drug in combination with PEG Intron (peginterferon alfa-2b) for a protected indication (see Ribavirin Response Letter)

- Amifostine with labeling that omitted a patent-protected indication (see Amifostine Response Letter)

- Dronabinol with labeling that omitted a patent-protected indication (see Dronabinol Response Letter)

- Ramipril with labeling that omitted a patent-protected indication and related clinical trial information (see Ramipril Response Letter)

Similarly, the possibility that a generic irinotecan product might be used off-label as second-line therapy in combination with 5-fluorouracil and leucovorin provides no basis for denying approval of an ANDA for irinotecan with this combination-use carved out. Requiring FDA to consider the safety and efficacy of a generic irinotecan product in the treatment of patients seeking to use irinotecan in combination with 5-fluorouracil and

leucovorin, either as a component of first-line or second-line therapy, where the generic does not seek approval for that indication, would effectively create new approval requirements beyond those established by Congress and the Agency. In addition, it would be inconsistent with our long-standing policy of not interfering with the practice of medicine, in particular with physicians' ability to prescribe approved drug products for their patients for any purpose deemed appropriate in their professional judgment.

Moreover, the request to carve out protected labeling from a generic irinotecan product can be distinguished from our refusal to carve out protected labeling for sirolimus. In our September 20, 2004, response to a citizen petition, we concluded that "the protected labeling in question contains extensive, critical prescribing information . . . that any physician should receive to appropriately determine treatment *for all indications* for sirolimus"[18] (emphasis added) (Sirolimus Response Letter at 3). Similarly, we concluded that the carved-out information was necessary for safe use even in the remaining, unprotected population (*id.* at 4). Here, by contrast, information regarding the protected information is not necessary to make irinotecan safe and effective for the remaining, second-line, non-protected conditions of use.

B. A Generic Drug Product With an Indication Carved Out in Accordance With the Act and FDA Regulations Is Not Misbranded Because Its Labeling Lacks the Carved-Out Indication.

You argue that we should further refuse to approve irinotecan ANDAs with carved-out labeling because such approved ANDAs would fail to comply with the misbranding provisions at 21 U.S.C. 352(a) (or section 502(a) of the Act), which state that a drug is misbranded if its labeling is "false or misleading in any particular." You state that under 21 U.S.C. 321(a)(2)(n) (presumably intending to cite section 201(n) of the Act (21 U.S.C. 321(n)), a product's labeling is misleading if it lacks information that is material with respect to consequences that may result from the use of a product as prescribed and under such conditions of use as are customary or usual. You further argue that any irinotecan ANDA that omits information related to the combination use of irinotecan is misleading because it fails to include information related to the use of irinotecan as prescribed and as used in its usual and customary manner. Thus, you maintain that any generic irinotecan product would be misbranded under sections 502(a) and 201(n) of the Act if it lacked information about this combination use (Petition at 12-14).

As we explained in our response to a similar argument in the Amifostine Response Letter, your interpretation of the misbranding provisions in sections 502(a) and 201(n) of the Act cannot be reconciled with a reading of the Act as a whole. If a carve-out of protected information that did not render a drug less safe and effective for the remaining, non-protected conditions of use would nonetheless render the drug misbranded for failure to include information pertinent to the carved-out use, the provisions permitting such carve-outs would be superfluous. To interpret these provisions as you do would be to read section 505(j)(2)(A)(viii) (permitting the ANDA applicant to decline to seek

[18] September 20, 2004, letter from William K. Hubbard, Associate Commissioner for Policy and Planning, to Michael S. Labson and Elizabeth M. Walsh, Docket No. 2003P-0518 (Sirolimus Response Letter).

approval for one or more patented conditions of use) out of the statute. Such a reading would be contrary to the fundamental canon that an individual statutory provision should be construed in the context of the statutory scheme in which it appears.[19] As stated previously, in authorizing the submission of a section viii statement, the Act allows an ANDA applicant to carve out from labeling a method of use claimed by a listed patent.

Although the Act requires that an ANDA contain information showing that the proposed conditions of use have been previously approved for the listed drug, the Act does not require that an ANDA be approved for each indication for which the reference listed drug is approved if an indication is protected by patent or exclusivity. Similarly, although the Act requires that the labeling of a generic drug be the same as the labeling approved for the listed drug, it provides an exception for changes resulting from the fact that the generic drug and the listed drug are produced or distributed by different manufacturers.

Your position—that the labeling for a generic irinotecan product with the carved-out indication is misleading under sections 502(a) and 201(n) of the Act because the drug will be prescribed off label for patients receiving first-line combination therapy—would effectively nullify the provisions in the Act that permit the approval of a generic drug with a carved-out indication. Conversely, our interpretation—that a generic drug product is not misbranded if its labeling omits an indication protected by patent—is consistent with the Act's provisions on ANDA patent certifications and sameness of conditions of use and labeling for generic products, yet still gives effect to statutory provisions regarding misbranding and adequate directions for use (in circumstances where the law does not specifically permit omission of protected information).

Moreover, unlike your interpretation of the misbranding provisions, our interpretation is consistent with the underlying goals of the Hatch-Waxman Amendments. The Hatch-Waxman Amendments provided sponsors of innovator drugs with marketing exclusivity and patent listing provisions which protect certain aspects of innovator drugs from generic competition for certain periods of time. As a quid pro quo for this increased protection, the Hatch-Waxman Amendments created an abbreviated approval mechanism allowing sponsors of generic drugs to rely on the Agency's findings of safety and effectiveness for innovator drugs in seeking approval of their generic drug products when intellectual property barriers to approval expire or are otherwise removed.

The Hatch-Waxman Amendments thus strike a balance between encouraging the research and development of new drugs and enabling the marketing of lower-cost, generic versions of those drugs at the earliest possible time. Under your interpretation of the misbranding provisions, the existence of patent protection for Camptosar's first-line indication or any combination use would prohibit the approval of a generic irinotecan product for any indication for the duration of the patent on the use of the drug in combination, thereby limiting the opportunity for consumers to benefit from the existence of lower-cost generic products, even for the non-protected second-line use of the product as monotherapy, during this period. On the other hand, our interpretation allows

[19] *See United Savings Ass'n v. Timbers of Inwood Forest Associates*, 484 U.S. 365, 371 (1988); *Gustafson v. Alloyd Co.*, 513 U.S. 561, 568 (1995).

innovators to enjoy the benefits associated with their efforts to develop new indications (including patent protection and exclusivity for those indications) while promoting competition with respect to indications for which innovators are not entitled to protection (either because they have not conducted research that entitles them to protection or because any applicable protection has expired, been successfully challenged, or has otherwise ceased to be a barrier to approval).

III. CONCLUSION

We have reviewed your petition and other relevant information available to us. For the reasons stated above, we deny your request that we refuse to approve any ANDA for an irinotecan HCl product with labeling that omits information on use of the drug in combination with 5-fluorouracil and leucovorin.

Sincerely,

Janet Woodcock
Director
Center for Drug Evaluation and Research